APOE E2 Carriers Showed Worse Associative Learning Than E3 Carriers in a Cognitively Normal Aging Han Chinese Population

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Research Article

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Abstract

Background: Polymorphism in the APOE gene has been shown to be associated with cognitive function, however, the related studies are not consistent. To investigate the relationship between *APOE* gene polymorphism and cognitive function, we conducted the current cross-sectional study specifically to investigate the effect of different *APOE* genotypes on cognitive performance in normal elderly adults

Methods: A total of 156 older adults with normal cognitive function were enrolled in the current study. According to different genetic types, they were divided into three groups: 1) E2/2 or E2/3 (APOE E2); 2) E3/3 (APOE E3); and 3) E2/4, E3/4, or E4/4 (APOE E4). Then Montreal Cognitive Assessment (MoCA) and Neuropsychological Test Battery (NTB) were used to assess their global cognitive function and domain-specific cognitive function, respectively.

Results: The results of Kruskai-Wallis H test showed that the scores of associative learning in APOE E2 group were lower than that in E3 groups ($p<0.05$), but there was no statistical difference ($p>0.05$) in associative learning between E2 group and E4 group, and E3group and E4 group. Similarly, there was no difference ($p>0.05$) in the global cognitive function among the three groups.

Conclusion: *APOE* E2 is associated with decreased associative learning function than *APOE* E3 in a cognitively normal aging Han Chinese population.

Introduction

Genetic variance might account for individual differences in adult cognitive function[1]. Apolipoprotein E (*APOE*), a gene implicated in the transport of cholesterol and other lipids between cellular structures[2], has been experiencing as the largest contributor to genetic risk for late onset Alzheimer's disease (AD)[3]. It is genetically associated with two single-nucleotide polymorphisms (SNPs) that mark three alleles ε4, ε3, and ε2[4]. And the ε4 allele has been demonstrated to increase associations between cerebral Aβ level and cognitive functioning in adults with dementia and healthy older adults[5,6]. Although considerable research has been done on ε4, ε2 has been seriously neglected because of its low allele frequency. Previous studies suggest that possession of a ε2 allele, prevalent in 15% of the population[7], is associated with a lower risk of AD, less AD neuropathology as well as a slower progression of vascular cognitive impairment[8-10]. However, a study [11]shows that possession of an ε2 allele is associated with poorer cognitive performance and more psychiatric symptoms in chronic, combat-related posttraumatic stress disorder (PTSD) subjects, while another study[12] also suggests that carriers of the e2 allele shows performance disadvantages in sustained attention. What's more, some studies have even identified the ε2 allele as a risk factor in dysbetalipoproteinemia[13], cerebral small-vessel disease[14], and aggressiveness of certain cancer[15]. Therefore, relevant research conclusions are not consistent.

Until now, only a few studies have been involved in the relationship between *APOE* gene polymorphism and cognitive function in Chinese normal cognitive elderly. For example, Zhen J[16] et al find that *APOE*

genotype might modify the risk for cognitive impairment in old age diabetes patients, and Su yy[17] et al prove that ε2 might as a protective factor in Chinese dialysis population since it might reduce the prevalence and of the onset age of depression. However, these above studies only focus on the general cognitive function of the subjects but neglect their specific cognitive areas, so we conducted this cross-section study to examine the relationship between the *APOE* ε2 allele and various cognitive fields (composed of global cognitive function and multiple domains of cognitive function) among the elderly with normal cognitive function in China

Methods

A total of 156 elderly people (male/female = 61/95) with normal cognitive function were included in the study. Sampling methods and processes have been described in detail in our previous study [18]. All participants met the following criteria: Han Chinese, aged 60 and over;

2) normal cognitive ability; 3) without major medical abnormalities (e.g. cancer and infection); 4) without serious mental illness (e.g. schizophrenia, and dementia); 5) willing to cooperate. A standardized questionnaire was utilized to collect these participants' general information (for example, age and education), daily living habits (smoking and drinking) and medical conditions (diabetes and hypertension).What's more, a completion of physical examinations, MRI scans and laboratory tests were also obtained for each subject.

All participants gave written consent to participating in this study. And the study was approved by the Research Ethical Committee of the affiliated mental health center of Shanghai jiaotong university school of medicine.

Clinical Assessment and Cognitive Assessment

The Neuropsychological Test Battery [consists of Digit span[19] (assess attention, working memory and executive function), Verbal fluency[20] (measure language ability related to executive function), Auditory verbal learning test[21] (assess learning ability, recognition memory and delayed free recall), Associative learning and visual identification test[22] (assess visual attention and processing speed), Webster picture completion[23] (evaluate executive function) and Webster block design[24] (assess visuospatial and executive function)] and the Montreal Cognitive Assessment (MoCA)[25] were used as tools to assess their specific cognitive domains and global cognitive ability, respectively.

APOE genotype and blood lipids

Genomic DNA was extracted from peripheral blood (Morning fasting whole blood) by using a Blood Genomic DNA Extraction Kit (Qiagen NV, Venlo, the Netherlands). *APOE* genotype was determined by allele-specific polymerase chain reaction (PCR) methodology[26]. Then these 156 subjects were divided into three groups according to different genotypes, *APOE* E2 (ε2/ε2 and ε2/ε3, n=25), *APOE* E3 (ε3/ε3,

n=106), and *APOE* E4 (ε2/ε4, ε3/ε4, and ε4/ε4, n=25). Table1 presents the detailed distribution of *APOE* genotypes. In addition, all participants were also tested for plasma glucose, cholesterol, triglycerides, high density lipoprotein and low density lipoprotein.

Data analysis

Continuous variables were expressed as mean ±SD and categorical variables were expressed as frequencies (%). One sample Kolmogorov-Smirrnov test was used to test whether the data conform to a normal distribution. Chi square test was utilized to compare categorical variables. One-way analysis of variance (ANOVA) Least—Significant Difference (LSD) was used to compare the differences among the *APOE* E2 group, *APOE* E 3 group, and *APOE* E 4 group (normal distribution data); while Kruskai-Wallis H test was used to compare data of non-normal distribution among three groups. Two-tailed tests were utilized in a significance level of $P<0.05$ for all analyses. All statistical analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA).

Results

Characteristic of subjects with different APOE genotypes

Table 1 presents the characteristic of subjects with different APOE genotypes. There was no difference ($p>0.05$) in education, age, BMI, gender, diabetes, hypertension, current smoking status, current drinking status, MoCA, Digit span, Immediate memory, Visual discrimination, Language fluency, Delayed memory, Wechsler mapping and Wechsler Block Map among the three groups. The results of Kruskai-Wallis H test (as the data did not conform to the normal distribution) showed that there were statistical differences ($p<0.05$) in Associative Learning among the three groups. Further comparisons revealed that the scores (6.240±3.163) of Associative Learning in *APOE* E2 group were lower than those (8.433±3.924) in *APOE* E3 group ($p<0.05$), while there was no significant difference ($p>0.05$) between *APOE* E2 group and *APOE* E4 group, and between *APOE* E3 and E4. Figure 1 and Table 2 show the results.

Discussion

In the present study, we investigated the effect of *APOE* gene polymorphism on cognitive performance in Chinese elderly with normal cognitive function. And found that E2 carriers had worse visual attention and processing speed ability than E3 carriers, while there was no difference between E2 and E4 carriers or E3 and E4 carriers.

There was no statistical difference in age, gender and education among the three groups. By using the Neuropsychological Test Battery and MoCA, we found that scores of association learning test in *APOE* E2 group (6.240±3.163) were significantly lower than that (8.433±3.924) in E 3 group. However, there was no statistical difference ($p>0.05$) between the E2 group and E4 group (orE3 and E4 group). What's more, there was also no significant difference in global cognitive function among the three groups.

Sinclair LI[27] et al found that E2 carriers had slightly better episodic memory and executive functioning than E3 and E4 carriers in early to mid-adult, but Palmer Allred ND[28] et al found E2 carriers had worse global cognitive function than E3 carriers. What's more, a large study[29] (total n=2013) of APOE genotype and cognitive decline conduct in 2014 found no association between either E2 or E4 status and cognitive change in five separate tests, even when split by age group. So these relevant research conclusions were not consistent, and the discrepancy may be explained by ethnic differences.

There are several mechanisms may explain why *APOE* E2 is associated with decreased associative learning function than *APOE* E3. First, *APOE* ε2 status may influence the risk and progression of tauopathy[30]. Second, *APOE* ε2 may increase the likelihood of vascular disease and lead to cognitive decline in specific areas[31]. Third, under metabolic stress, *APOE* E2 homozygote may cause dysbetalipoproteinaemia in adults owing to impaired binding of remnant lipoproteins to heparan sulphate proteoglycans as well as the (low density lipoprotein) LDL receptor and related proteins[32] . Fourth, *APOE* E2 is correlated with increasing brain white matter hyperintensities (WMHs)[14], which is associated with neurologic decompression sickness, lower neurocognitive test performances as well as repetitive non-hypoxic hypobaric exposure[3334].

We have to admit that there are some limitations in our research. First, this is only a cross-sectional study, and we cannot establish a causal link between *APOE* E2 and associative learning function. Second, relatively small sample size reduces the reliability of research. Therefore, a large sample of longitudinal research is needed to further verify the above conclusion

Conclusions

In conclusion, *APOE* E2 is associated with reduced associative learning function than *APOE* E3 in healthy elderly. However, this conclusion needs to be verified by a larger sample of longitudinal study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of Declaration of Helsinki, and approved by the Research Ethical Committee of the affiliated mental health center of Shanghai Jiaotong University School of Medicine. All participants had signed the informed consent written informed consent before the start of the study.

Consent for publication

Not applicable.

Availability of data and materials

The data base generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

"L.W . and L.Y wrote the main manuscript text and S.F. and L.X prepared figure 1."

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Tables

Table1. Characteristics of subjects with different APOE groups

Characteristics	APOE E2 (n=25)	APOE E3 (n=106)	APOE E4 (n=25)	F	P
Age, y	70.40±8.067	70.01±7.786	68.56±6.436	0.445	0.642
Education, y	8.52±4.445	9.85±4.124	10.68±2.673	1.901	0.153
BMI, Kg/m^2	24.22±3.037	24.09±3.448	24.35±3.504	0.068	0.934
Male,n (%)	11(7.1)	40(37.7)	10(40.0)	0.169	0.845
Hypertension, n(%)	14(56.0)	53(50.0)	12(48.0)	0.184	0.832
Diabetes, n(%)	2(8.0)	10(9.4)	3(12.0)	0.119	0.888
Smoker, n(%)	6(24.0)	26(24.5)	3(12.0)	0.926	0.398
Drinker, n(%)	6(24.0)	22(20.8)	2(8.0)	1.288	0.279
MoCA	23.48±4.575	25.39±3.643	25.56±2.800	2.923	0.057
Digit span	13.56±4.144	14.50±3.865	14.28±3.273	0.612	0.543
Immediate memory	46.20±10.607	41.60±11.601	43.39±12.033	1.672	0.191
Associative Learning	6.240±3.163	8.433±3.924	7.646±3.746	3.475	0.033*
Visual discrimination	17.92±4.272	17.41±3.590	16.68±3.544	0.588	0.557
Language fluency	27.68±8.620	28.97±7.924	27.60±6.416	0.488	0.615
Delayed memory	22.40±9.574	21.50±8.674	22.32±8.778	0.159	0.853
Wechsler mapping	10.32±4.120	10.90±3.713	10.80±3.764	0.234	0.791
Wechsler Block Map	28.83±8.499	28.64±8.597	29.92±6.819	0.240	0.787

Note: Three groups were divided according to APOE genotypes: e2/2 or e2/3 (APOE e2); e3/3 (APOE e3); and e2/4, e3/4, or e4/4 (APOE e4). * means $p< 0.05$; Abbreviations: BMI, body mass index; MoCA, Montreal Cognitive Assessment

Table 2. Multiple comparisons among three groups

Variables	Group 1	Group 2	mean deviation	Standard error	p	95% CI
Associative Learning	APOE E2	APOE E3	-2.193	0.843	0.010*	-3.86~-0.53
		APOE E4	-1.406	1.082	0.196	-3.54~-0.73
	APOE E3	APOE E4	0.787	0.857	0.360	-0.91~2.48

Figures

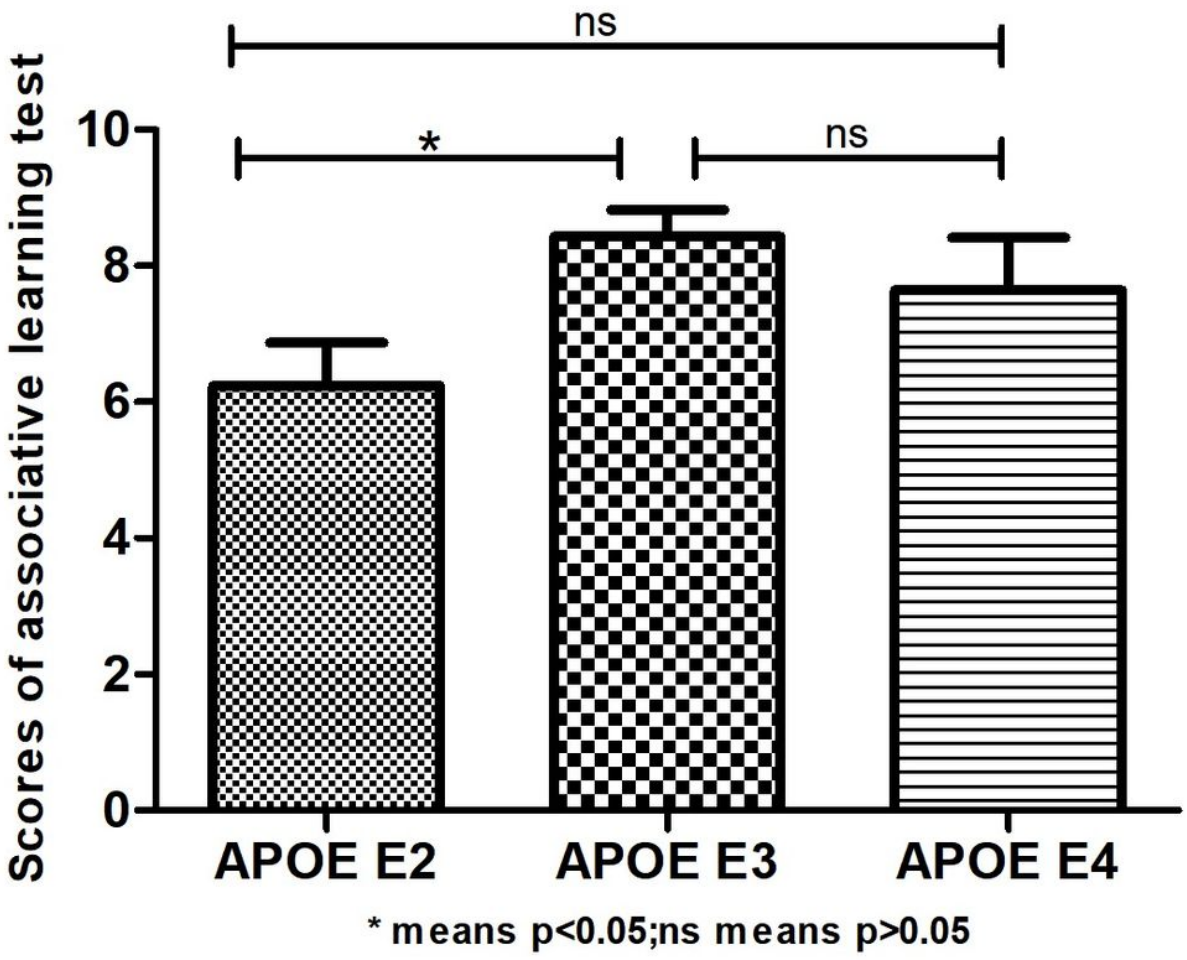

Figure 1

Further comparisons revealed that the scores (6.240±3.163) of Associative Learning in APOE E2 group were lower than those (8.433±3.924) in APOE E3 group ($p<0.05$), while there was no significant difference ($p>0.05$) between APOE E2 group and APOE E4 group, and between APOE E3 and E4.